CASE REPORT

A case of ovarian growing teratoma syndrome treated by cytoreductive surgery

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Abstract Ovarian growing teratoma syndrome (GTS) is a rare disease characterized by growth of a benign tumor during or after chemotherapy, following the removal of germ cell gonadal cancers. Although benign, GTS tumors grow gradually and may compress surrounding organs. In addition, up to 3% of GTS cases can undergo malignant transformation. It is, therefore, needed to treat GTS. No standardized management protocol has been established to treat GTS; however, surgical resection is likely the only effective treatment because tumors in GTS are resistant to chemotherapy and radiation therapy. However, complete resection with conventional procedures is sometimes difficult when peritoneal metastasis is widespread. We report a rare case of ovarian GTS with widespread peritoneal metastases, which was totally resected by peritonectomy procedures. A 45-year-old Japanese woman was initially diagnosed with an immature teratoma grade 3, which was treated by hysterectomy and bilateral salpingo-oophorectomy. Adjuvant chemotherapy was performed after surgery with bleomycin, etoposide, cisplatin, and other

chemotherapies. Due to recurrence of a chemoresistant tumor and normalization of tumor markers, GTS was suspected. She was referred to our institute, and complete cytoreductive surgery was performed using peritonectomy procedures, including parietal peritoneal resection, greater omentectomy, lesser omentectomy, rectosigmoid colectomy, diaphragm dissection, and cholecystectomy. A complete cytoreduction with no visible residual tumor tissue was achieved.

Keywords Ovarian growing teratoma syndrome · Immature teratoma · Cytoreductive surgery · Peritonectomy · Ovarian tumor

Introduction

Ovarian growing teratoma syndrome (GTS) is a rare disease characterized by growth of a benign tumor during or after chemotherapy, following the removal of germ cell

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gonadal cancers. A review of the literature in 2016 by Song Li et al. reported 101 published cases of ovarian GTS after an ovarian malignancy [1]. The case reports concerning this disease may be attributed to the increased awareness of this syndrome, improved diagnostic imaging tools, and the efficacy of chemotherapeutic agents, which appear to play a significant role in the etiology of this syndrome.

Although GTS entails development of benign tumors, GTS tumors grow gradually and may compress surrounding organs. In addition, up to 3% of GTS cases can undergo malignant transformation [2]. It is, therefore, needed to treat GTS.

Generally, cases with widespread intra-abdominal dissemination are treated with surgery and adjuvant chemotherapy or radiation therapy to remove residual tumors because resecting all intra-abdominal dissemination is difficult with conventional procedures. However, because GTS is resistant to chemotherapy and radiation therapy, only follow-up studies have been conducted to evaluate residual GTS tumors.

Sugarbaker proposed a procedure involving the removal of visible tumors in the abdomen, the lining of the abdomen, and affected organs [3]. Complete surgical resection not only provides relief of pressure and mass effect, but also provides confirmation of the diagnosis of GTS and exclusion of recurrence of malignancy.

Herein, we report a rare case of ovarian GTS with widespread peritoneal metastasis, which was completely resected by cytoreductive surgery using peritonectomy procedure.

Case report

A 45-year-old Japanese woman (gravida 2, para 2) was referred to the Peritoneal Surface Malignancy Center at Kusatsu General Hospital (Shiga, Japan). She was initially diagnosed with left ovarian immature teratoma Stage IIIB, which was treated with hysterectomy and bilateral salpingo-oophorectomy 4 years before she visited our hospital (Fig. 1a). In this patient, serum HCG and AFP levels were 213 mIU/mL and 246.7 ng/mL, respectively, before initial treatment of the immature teratoma. Histopathological examination showed proliferation of variably sized nests composed of small round cells. These neoplastic cells had round to oval nuclei with small nucleoli and scant cytoplasm. Rosette formation was noted, and mitotic figures were scattered. Mature skin tissue was also noted, and more than half of the tumor was composed of immature neuroepithelial tissue (Fig. 1b). Therefore, a diagnosis of immature teratoma grade 3 was made.

Adjuvant chemotherapy with bleomycin, etoposide, and cisplatin over four cycles was performed. HCG lowered to 50 mIU/mL 2 months after surgery. The patient presented to

Fig. 1 a Resected original ovarian tumor, including left ovary (1410 g) and uterus + right ovary (150 g). b LPF of resected specimen of original ovarian immature teratoma, grade 3, variably sized nests composed of small round cells co-exist with mature stratified squamous epithelium (HE). HE hematoxylin–eosin, LPF low power field

the hospital 9 months after surgery with severe bloating, and a CT scan revealed massive peritoneal dissemination in the abdomen. Two cycles of paclitaxel, ifosfamide, and cisplatin were added. This regimen was then changed to carboplatin and paclitaxel over four cycles due to renal impairment. Further six cycles of carboplatin and etoposide were then performed. F-18-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) showed no accumulation lesions, although a CT scan showed peritoneal dissemination in pelvic and liver surfaces after these chemotherapies. The serum HCG was within normal range. Due to the presence of a chemoresistant tumor and the normalization of tumor markers, GTS was suspected. The CT scan showed gradual growth of peritoneal tumors. Finally, the patient was referred to our institute with the aim of complete resection of the peritoneal metastases.

The patient was asymptomatic. Imaging—including CT and magnetic resonance imaging (MRI)—showed a low-density mass in the liver surface and massive peritoneal

Fig. 2 **a** Right diaphragm lesion. **b** Tumors in paracolic gutters, right parietal peritoneum, and ascending colon

dissemination. Complete cytoreductive surgery (CRS) was performed 51 months after initial surgery. After the abdominal wall was open, no ascites was found. A peritoneal washing cytological study did not reveal malignant cells. Multiple tumors—with diameters ranging from 1 to 2 cm—were located from the rectum to the sigmoid colon, pelvis, and all over the parietal peritoneum, except the left diaphragm, the small bowel, and its mesentery (Fig. 2a, b). CRS was performed using Sugarbaker peritonectomy procedures, including parietal peritoneal resection (except for the left diaphragm peritoneum), greater omentectomy, lesser omentectomy, rectosigmoid colectomy, and cholecystectomy [3]. A complete cytoreduction, with no visible residual tumor tissue, was achieved. Histopathological study of the peritoneal disseminated lesions and the tumor on the diaphragm revealed the presence of mature skin tissue and skin appendages (Fig. 3a–d). No immature neuroepithelial components were observed. Accordingly, a final diagnosis of GTS was made.

The patient's postoperative hospital stay was unremarkable. After a follow-up of 8 months, she had no recurrence.

Discussion

GTS was originally defined by DiSaia et al. in 1977 as a rare disease characterized by growth of a benign tumor following the removal of germ cell gonadal cancers during or after chemotherapy [4]. Currently, the following diagnostic criteria are used according to the Logothetis definition: (1) normalization of serum HCG and AFP, (2) enlarging or new masses despite appropriate chemotherapy for nonseminomatous germ cell tumors, and (3) the exclusive presence of a mature teratoma in the resected specimen [5].

There are three hypotheses for the pathogenesis of GTS. The first hypothesis is that chemotherapy transforms malignant cells into benign teratomatous elements. The second hypothesis is that chemotherapy can only destroy malignant cells, leaving chemoresistant teratomas behind [3, 8, 9]. The third hypothesis is an inherent and spontaneous differentiation of malignant cells into benign tissues, as suggested by the experimental murine teratocarcinoma mouse model [6].

The incidence of GTS after ovarian germ cell neoplasia has been reported to range from 2.5 to 11.7% [5, 6]. The median age at initial diagnosis of GTS is 24 years [7]. The median interval between diagnosis of immature teratoma and that of GTS is 9 months [8].

Risk factors reported for development of GTS include incomplete resection of the primary tumor, initial tumor histology containing mature teratoma elements, histological grades 2 and 3, surgical stages III and IV, and no decrease in initial tumor bulk after treatment with adjuvant chemotherapy [3, 11, 12].

No standardized management protocol has been established to treat GTS; however, surgical resection is likely the only effective treatment because tumors in GTS are resistant to chemotherapy and radiation therapy. CRS techniques for widespread peritoneal involvements were first reported by Sugarbaker [3]. The original cytoreductive approach may require six peritonectomy procedures to resect or strip cancer from all intra-abdominal surfaces. These are greater omentectomy–splenectomy, left upper quadrant peritonectomy, right upper quadrant peritonectomy, lesser omentectomy–cholecystectomy with stripping of the omental bursa, pelvic peritonectomy with sleeve resection of the sigmoid colon, and antrectomy. Long-term, disease-free survival in selected patients has been achieved with this cytoreductive approach to treating peritoneal carcinomatosis or mesothelioma. This procedure can be used for complete resection of GTS.

Chua et al. reviewed the morbidity and mortality rates from CRS based on 24 studies [9]. The frequency of more than grade III was 28.8%. The main risks of CRS are re-

Fig. 3 **a** Mature teratoma of the peritoneum (HE, LPF). **b** HPF of 3A, adipose tissues, squamous cell, and sebaceous gland (HE). **c** HPF of 3A, ganglion cells (HE). **d** HPF of 3A, nerve fibers (HE). *HE* hematoxylin–eosin, *LPF* low power field, *HPF* high power field

operation, sepsis, fistula, abscess, hematological toxicity, ileus, renal insufficiency, perforation, deep vein thrombosis, and anastomotic leak. Overall, the mean mortality rate was 2.9%. Considering these risks, CRS with hyperthermic intraperitoneal chemotherapy is now recommended, with acceptable risks [10].

Most cases in the literature of ovarian GTS have been resected through laparotomy; however, recently, four case reports of successful laparoscopic excisional surgery of ovarian GTS have been reported [11]. In addition to many well-known advantages over laparotomy—including less blood loss, less pain, shorter recovery periods, and less adhesion formation—for the sake of any future pregnancy, laparoscopic surgery should play an important role in surgical therapy for GTS because it minimizes intra-abdominal adhesion formation and the risk of infertility [12–14]. Laparoscopic surgery may be an effective alternative diagnostic and therapeutic method. However, we should wait for further study, given that only four reported cases have been managed laparoscopically so far.

Prognosis and overall survival rate varies depending on reports; only 101 cases of GTS from ovarian immature teratoma have been reported. Spiess et al. reported a high recurrence rate of 72–83% in patients with partial resection against 0–4% in those who underwent complete resection [15]. The case series reported local recurrence rates between 0 and 54% [10]. The completeness of the

resections, which would likely relate to the complexity of the presenting lesion and the surgeon's expertise, may account for these differences.

Bentivegna et al. reported 38 cases of surgical outcomes after debulking surgery for intra-abdominal ovarian GTS [16]. A complete macroscopic resection was performed in 25 cases. During a median follow-up period of 73 months after initial treatment of GTS, 10 of 38 (26%) patients had recurrences. Among the ten patients with recurrence, eight underwent complete macroscopic resection. Although recurrence rate varies depending on report, GTS recurrences were frequent in their study even after complete resection (32% recurrence rate). Therefore, they suggested that considering the good prognosis for GTS after the initial management of immature ovarian teratoma and the high recurrence rate even after complete surgery, whenever technically possible, a fertility-preserving surgery leaving the uterus in place and at least a part of one ovary should be performed.

We reported a case of GTS in a 45-year-old Japanese woman with widespread peritoneal metastasis. A complete cytoreduction with no visible residual tumor tissue was achieved. Resected specimens showed no immature tissue, which appears to support the hypothesis that chemotherapy damages and destroys malignant cells, leaving chemoresistant teratoma behind. Considering the median recurrence-free interval from final treatment of GTS to recurrent GTS is about 24 months, an 8-month follow-up in this case

was not enough [11]. Continuous follow-up is necessary to monitor for recurrence. The mechanism, diagnoses, and treatment of GTS is still controversial because of the limited number of cases, and all evidence available in the literature is based on case reports and series. CRS should be one of the treatment modalities despite the high incidence of complications with CRS, because survival rates could be improved with cautious perioperative management in selected patients. Further study is required to standardize optimal therapy about GTS.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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